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(54) Title: PROCESS FOR THE PREPARATION OF 2,3,5-TRIMETHYLHYDROQUINONE DIACYLATES

(57) Abstract: 2,3,5-Trimethyl-1,4-hydroquinone diacylates are obtained by reacting 3,5,5-trimethyl-1,4-benzoquinone with an acylating agent in the presence of methane trisulfonic acid as a catalyst.

Process for the preparation of 2,3,5-trimethylhydroquinone diacylates

The present invention is concerned with a process for the preparation of 2,3,5-trimethylhydroquinone diacylates by reacting 3,5,5-trimethyl-1,4-benzoquinone (ketoisophorone) with an acylating agent in the presence of methanetrisulfonic acid. 2,3,5-Trimethylhydroquinone diacylates are useful as reactants for the preparation of 2,3,5-trimethylhydroquinone, itself a known valuable reactant for the preparation of (all-rac)-α-tocopherol.

2,3,5-Trimethylhydroquinone diacylates are known to be producible by reacting ketoisophorone with an acylating agent in the presence of a strongly acidic catalyst. Many such catalysts have been proposed in the past for this purpose, in particular protonic acids, e.g. such inorganic acids as sulphuric acid; such organic acids as p-toluenesulphonic acid; strongly acidic ion exchange resins; and such Lewis acids as zinc chloride, boron trifluoride, antimony pentafluoride and titanium tetrachloride: see inter alia German Offenlegungsschrift 2149159 and European Patent Publications EP 0916642 A1 and EP 1028103 A1; as well as NH-acidic or CH-acidic catalysts, see PCT Publication WO 03/051812.

It has now been found that by the use of small amounts of methanetrisulfonic acid, the conversion of ketoisophorone to 2,3,5-trimethylhydroquinone diacylates can be accomplished in high yield and without the need to use additional solvents. The use of methanetrisulfonic acid as the catalyst provides, all in all, advantages over catalysts used so far in this reaction in terms of stability of the catalyst, high yield, selectivity, and costs.

Thus, the presence invention relates to a process for the preparation of 2,3,5-trimethyl-1,4-hydroquinone diacylates by reacting 3,5,5-trimethyl-1,4-benzoquinone with an acylating agent in the presence of methane trisulfonic acid.

The acylating agent used in the process of the present invention may be any acylating agent that is conventionally used in the conversion of ketoisophorone to 2,3,5-trimethylhydroquinone acylates, particularly acid anhydrides, acyl halides, and enol esters. Examples of acid anhydrides are straight or branched chain alkanoic acid anhydrides such as acetic, propionic and butyric anhydride. Examples of acyl halides are straight or branched chain alkanoyl chlorides such as acetyl, propionyl and butyryl chloride. Finally, examples of enol esters are isopropenyl acetate and butyrate. The preferred acylating agent is acetic anhydride or acetyl chloride, especially acetic anhydride.

The process of the present invention can be carried out in the absence of a solvent. While the ratio of acylating agent to ketoisophorone is not narrowly critical the molar ratio of acylating agent to ketoisophorone is suitably from about 1 : 1 to about 10 : 1, preferably from about 5 : 1 to about 3 : 1, and is most preferably about 3 : 1.

The amount of catalyst, methane trisulfonic acid, is suitably about 0.01 to about 2.0 mole%, preferably about 0.075 to about 1.5 mole%, and most preferably about 0.1 to about 1.0 mole%, based on the amount of ketoisophorone.

The process is conveniently carried out at temperatures from about 0 °C to about 140 °C, preferably from about 20 °C to about 90 °C, especially 20 °C to 70 °C.

The process according to the present invention may be carried out batchwise or in continuous mode. Moreover, the process is conveniently carried out under an inert gas atmosphere, preferably under gaseous nitrogen or argon.

The progress of the reaction is suitably monitored by gas chromatography and mass spectrometry of samples taken from the reaction mixture at various time intervals during the reaction.

The produced 2,3,5-trimethylhydroquinone diacylate can be isolated after distilling off the remaining acylating agent and the secondary product formed in the acylation, e.g. acetic acid when acetic anhydride is used as the acylating agent, by extraction of the crude product mixture with a suitable organic solvent, e.g. toluene. For instance, in effecting this procedure using acetic anhydride as the acylating agent 2,3,5-trimethylhydroquinone diacetate was obtained as colourless crystals after evaporating off the toluene used as the extracting solvent. Another isolation procedure is the crystallization of the 2,3,5-trimethylhydroquinone diacylate from the mixture at the termination of the reaction by cooling, and, optionally, adding water, to the mixture to promote the crystallization.

The catalyst can be recovered by extraction with water or acid-water and concentration of the extract. Alternatively, the catalyst can be recovered by adding a

biphasic solvent system, e. g. a carbonate (particularly ethylene carbonate or propylene carbonate) and an aliphatic hydrocarbon (particularly heptane or octane), and isolating it from the polar (carbonate) phase

The 2,3,5-trimethylhydroquinone diacylate obtained by the process of the present invention can be converted into 2,3,5-trimethylhydroquinone by transesterification, i.e. by treatment with an alcohol, e.g. an aliphatic alcohol such as isopropanol or n-butanol. Depending on the amounts of alcohol and catalyst and on the temperature in the reaction mixture, the transesterification yields the unesterified 2,3,5-trimethylhydroquinone and the ester formed as the further product. 2,3,5-Trimethylhydroquinone can be converted into (all-rac)-α-tocopherol by known procedures by reaction with isophytol, preferably in a biphasic solvent system, e.g. in a solvent system comprising a polar solvent such as ethylene or propylene carbonate, and an non-polar solvent, particularly an aliphatic hydrocarbon such as heptane, see, e.g. international application PCT/EP03/01556.

The invention is illustrated further by the following Examples.

Example 1

A 50-ml four-necked flat-bottomed flask equipped with a thermometer, a glass-tube (Ø 5 mm) for Ar-purge, a reflux condenser and a magnetic stirring bar was charged with methanetrisulfonic acid (see Table 1 below) and 10.324 g (66 mmol) of ketoisophorone. Within 2 min, acetic anhydride was added dropwise (see Table 1 below) under rapid stirring. During addition, the mixture turned dark yellow to finally dark brown and the internal temperature increased. After cooling to the desired reaction temperature that temperature was maintained by means of an oil bath. Samples were withdrawn and submitted to qualitative GC-analysis. After the reaction time (see Table 1 below), the reaction mixture was cooled to room temperature and the catalyst was deactivated by addition of 3.7 g (70 mmol) anhydrous sodium carbonate. The reaction mixture was concentrated by 40°C/10mbar thereby distilling off acetic acid and unreacted anhydride. The crude product was analyzed by GC using squalane as internal standard. The results and reactions conditions are given in Table 1 below:

Table 1

(Ac_2O) [mmol]	$(SO_3H)_3CH$ [mg]	$(SO_3H)_3CH$ [mol %]	T [°C]	time [h]	conversion [%]	TMHQ-DA [%]
200	171.2	1.0	25	4	97.2	91.8
333	171.2	1.0	25	4	99.3	91.1
666	171.2	1.0	25	4	99.2	94.0
200	93.5	0.55	25	22	78.6	69.0
200	171.2	1.0	25	22	100	96.6
200	342.4	2.0	25	22	100	93.2
200	120	0.7	60	4	99.1	91.5
200	120	0.7	60	4	99.3	92.9
200	120	0.7	60	4	98.9	92.3
200	34.2	0.2	70	4	83.5	72.2
200	94.2	0.55	70	4	100	92.6
200	154.1	0.9	70	4	100	94.2
200	171.2	1.0	40	4.5	98.8	88.2
200	342.4	2.0	40	3.5	100	90.0

The values given are averages from several measurements (two or three) and two experiments.

Ac_2O : acetic anhydride; TMHQ-DA : 2,3,5-trimethyl-1,4-hydroquinone diacetate [yield]

Example 2

Using a 230 ml-flask the procedure of Example 1 was repeated with changing ratios of ketoisophorone and acetic anhydride. The reaction conditions and results are given in Table 2 below:

Table 2

(Ac_2O) [mmol]	KIP/Ac_2O [ratio]	T [°C]	time [h]	conversion [%]	TMHQ-DA [%]	S(TMHQ-DA) [%]
299	1 : 2.25	45	12	89.7	85.8	95.6
332	1 : 2.5	45	12	91.9	87.2	94.9
398	1 : 3	45	12	95.6	90.9	95.1
663	1 : 5	45	12	98.6	94.5	95.8
1327	1 : 10	45	12	98.1	93.0	94.8
398	1 : 3	25	24	83.6	80.6	96.3

The values given are averages from several measurements (two or three) and two experiments. S : Selectivity.

Example 3

In analogy to the procedure of Example 1, the reaction conditions were optimized using a statistical model (STAVEX). 20.32 g (200 mmol) of acetic anhydride were added within 10 min. to10.324 g (66 mmol) of ketoisophorone. The results are tabulated in Table 3 below:

Table 3

$(SO_3H)_3CH$ [mg]	$(SO_3H)_3CH$ [mmol]	$(SO_3H)_3CH$ [mol %]	T [°C]	time [h]	conversion [%]	TMHQ-DA [%]
17.2	0.07	0.1	25	4	0	0
17.4	0.07	0.1	100	4	43.2	14.8
172.5	0.67	1.0	100	4	100	83.5
85.6	0.33	0.5	40	14	97.6	89.7
17.2	0.07	0.1	25	24	10.8	1.0
85.5	0.33	0.5	55	14	100	90.3
85.5	0.33	0.5	55	22	100	91.4
171.4	0.67	1.0	25	4	83.9	75.6
85.6	0.33	0.5	85	14	100	89.6
17.1	0.07	0.1	100	24	45.6	16.4
34.4	0.13	0.2	55	14	88.7	79.0
85.5	0.33	0.5	55	6	99.5	90.4
171.1	0.67	1.0	25	24	99.3	92.7
154.2	0.60	0.9	55	14	100	91.3
171.4	0.67	1.0	100	24	100	84.6
171.3	0.67	1.0	60	7	100	91.2
128.1	0.50	0.8	60	10	100	91.9
85.5	0.33	0.5	60	12	100	93.5

Example 4

Based on the results of Example 3, experiments under optimized conditions were carried out. The results are summarized in Table 4

Table 4

(Ac_2O) [mmol]	KIP/ Ac_2O ratio	$(SO_3H)_3CH$ [mol %]	T [°C]	time [h]	conversion [%]	TMHQ-DA [%]	S(TMHQ-DA) [%]
398	1 : 3	0.5	60	6	97.4	92.0	94.5
663	1 : 5	1.0	25	24	100	96.7	96.7

What is claimed is:

1. Process for the preparation of 2,3,5-trimethyl-1,4-hydroquinone diacylates by reacting 3,5,5-trimethyl-1,4-benzoquinone with an acylating agent in the presence of methane trisulfonic acid.

2. A process as in claim 1 wherein the reaction is carried out in the presence of about 0.01 mol% to about 2 mol% of methane trisulfonic acid, based on 3,5,5-trimethyl-1,4-benzoquinone.

3. A process as in claim 2 wherein the reaction is carried out in the presence of about 0.1 mol% to about 1 mol% of methane trisulfonic acid, based on 3,5,5-trimethyl-1,4-benzoquinone.

4. A process as in any one of claims 1-3 wherein the molar ratio of acylating agent to 3,5,5-trimethyl-1,4-benzoquinone to is about 10 to 1, preferably about 3 to 1.

5. A process as in any one of claims 1-4 wherein the acylating agent is acetic anhydride.

6. A process as in any one of claims 1-5 wherein the reaction is carried out at about 0 °C to about 140 °C, preferably at about 20 °C to about 70 °C.

7. A process as in any one of claims 1-6 wherein the 2,3,5-trimethyl-1,4-hydroquinone diester obtained is converted in a manner known per se to α-tocopherol.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C67/08 C07C69/017 C07C69/16 C07D311/72

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DE 21 49 159 A (EASTMAN KODAK CO.) 6 April 1972 (1972-04-06) cited in the application claims 1-9	1-7
Y	US 6 103 924 A (N. SHI ET AL.) 15 August 2000 (2000-08-15) claims 1-21	1-7
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	M. SCHNEIDER ET AL.: "Industrial application of Nafion-systems in rearrangement-aromatisation, transesterification, alkylation, and ring-closure reactions" APPLIED CATALYSIS A GENERAL, vol. 220, no. 1-2, 2001, pages 51-58, XP002317570 the whole document	1-7
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